



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

--000:0:000--

In re Application of

Toyoaki ISHIKURA, et al.

Group Art Unit: 1624

Serial No. 10/500,071

Examiner: Bruck Kifle

Filed: June 25, 2004

Docket No.: 40072-0009

Title: AMORPHOUS SUBSTANCE OF TRICYCLIC TRIAZOLOBENZAZEPINE  
DERIVATIVE

--000:0:000--

Honorable Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Toyoaki ISHIKURA, the undersigned, do hereby declare:

1. THAT I am a co-inventor of the invention described and  
claimed in the above patent application.

2. THAT the following experiments were conducted under my  
direction and control:

(1) Preparation of Crystalline Compound A

A light yellow powder produced according to the method  
described in Example 20 of WO 99/16770 was dissolved in  
methylene chloride to prepare a solution which was then  
recrystallized from methanol to give crystalline compound A.

The crystalline compound A thus obtained was used in the following experiments.

(2) Subject to Lyophilization Method

The crystalline Compound A (1.5g) was dissolved in dimethylsulfoxide (8.5g) to prepare a solution which was then added dropwise into a 0.5% aqueous solution of hydroxypropylmethylcellulose TC-5R (manufactured by The Shin-Etsu Chemical Co., Ltd.) to produce a solid. The solid product was lyophilized at  $-10^{\circ}\text{C}$  to give a powder of the product.

The powder did not show the random noise (halo pattern) of amorphous materials as analyzed by powder X-ray diffractometry according to the same manner as described in the specification above on page 9, line 27 to 35 (see attached Chart 1).

(3) Subject to Extruder

(a) Test 1

The mixture of one part by weight of the crystalline Compound A and three parts by weight of hydroxypropylmethylcellulose TC-5R was charged at 30g/min into an extruder (Laboruder Mark II manufactured by the Japan Steel Works, Ltd.). The kneading condition was at  $180^{\circ}\text{C}$  and 210rpm and pure water was charged in the extruder at 10.5g/min.

(b) Test 2

The mixture of one part by weight of the crystalline Compound A and three parts by weight of hydroxypropylmethylcellulose TC-5R was charged at 30g/min into an extruder (Laboruder Mark II manufactured by the Japan Steel Works, Ltd.). The kneading condition was at  $180^{\circ}\text{C}$  and 210rpm and pure water was charged in the extruder at 7.0g/min.

(c) Test 3

The mixture of one part by weight of the crystalline Compound A and the same part by weight of

hydroxypropylmethylcellulose TC-5R was charged at 30g/min into an extruder (Laboruder Mark II manufactured by the Japan Steel Works, Ltd.). The kneading condition was at 120°C and 210rpm and pure water was charged in the extruder at 10.5g/min.

(d) Test 4

The mixture of one part by weight of the crystalline Compound A and the same part by weight of hydroxypropylmethylcellulose TC-5R was charged at 30g/min into an extruder (Laboruder Mark II manufactured by the Japan Steel Works, Ltd.). The kneading condition was at 120°C and 210rpm and pure water was charged in the extruder at 7.0g/min.

(e) Powder X-ray Diffractometry

The powders obtained by Tests 1 and 2 above did not show the random noise (halo pattern) of amorphous materials as analyzed by powder X-ray diffractometry according to the same manner as described in the specification above on page 9, line 27 to 35.

Further, the powder obtained by Tests 3 and 4 above still showed characteristic diffraction peaks as analyzed by powder X-ray diffractometry according to the same manner as described in the specification above on page 9, line 27 to 35 (see attached Chart 2).

(4) Subject to Solvent Distilling-off Method

(a) Test 1

A 15% (wt/wt) solution of Compound A in dimethylsulfoxide was evaporated under reduced pressure to give a powder.

(b) Test 2

The mixture of one part of a 15% (wt/wt) solution of Compound A in dimethylsulfoxide and 0.2 part of hydroxypropylmethylcellulose TC-5R was evaporated under reduced pressure to give a powder.

(c) Test 3

The mixture of one part of a 15% (wt/wt) solution of

Compound A in dimethylsulfoxide and 0.5 part of hydroxypropylmethylcellulose TC-5R was evaporated under reduced pressure to give a powder.

(d) Test 4

The mixture of one part of a 15% (wt/wt) solution of Compound A in dimethylsulfoxide and 0.5 part of methylcellulose was evaporated under reduced pressure to give a powder.

(e) Powder X-ray Diffractometry

The powders obtained by Tests 1 to 4 above did not show the random noise (halo pattern) of amorphous materials as analyzed by powder X-ray diffractometry according to the same manner as described in the specification above on page 9, line 27 to 35 (see attached Chart 3).

(5) Subject to Comminution

(a) The crystalline Compound A (20g) was charged into a ball mill machine (TI-300, manufactured by C.M.T. Kagaku, Ltd) having a 100mL pot of abrasion resistant alumina with twenty 20mm-diameter balls of abrasion resistant alumina. The milling was conducted for 10, 20 and 30 minutes as Tests 1, 2 and 3.

(b) The milling processes were conducted in the same manner as the above provided that 0.2 part of hydroxypropylmethylcellulose TC-5R was added with the crystalline Compound A. The milling was conducted for 10, 20 and 30 minutes as Tests 4, 5 and 6.

(c) The powders obtained by Tests 1 to 6 above did not show any characteristic diffraction peak as analyzed by powder X-ray diffractometry according to the same manner as described in the specification above on page 9, line 27 to 35 (see attached Chart 4).

However, after the storage at 60°C for one (1) week, they gradually crystallize again (see attached Chart 5).

As a comparison, the powder of Compound A produced in Example 1 described in the specification above on page 10, lines 7 to 16 was kept at 60°C for two (2) weeks. After

the storage, the powder of Example 1 did not show any characteristic diffraction peak as analyzed by powder X-ray diffractometry.

3. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: March 22 , 2006

Toyoaki Ishikura  
Toyoaki ISHIKURA

Chart 1

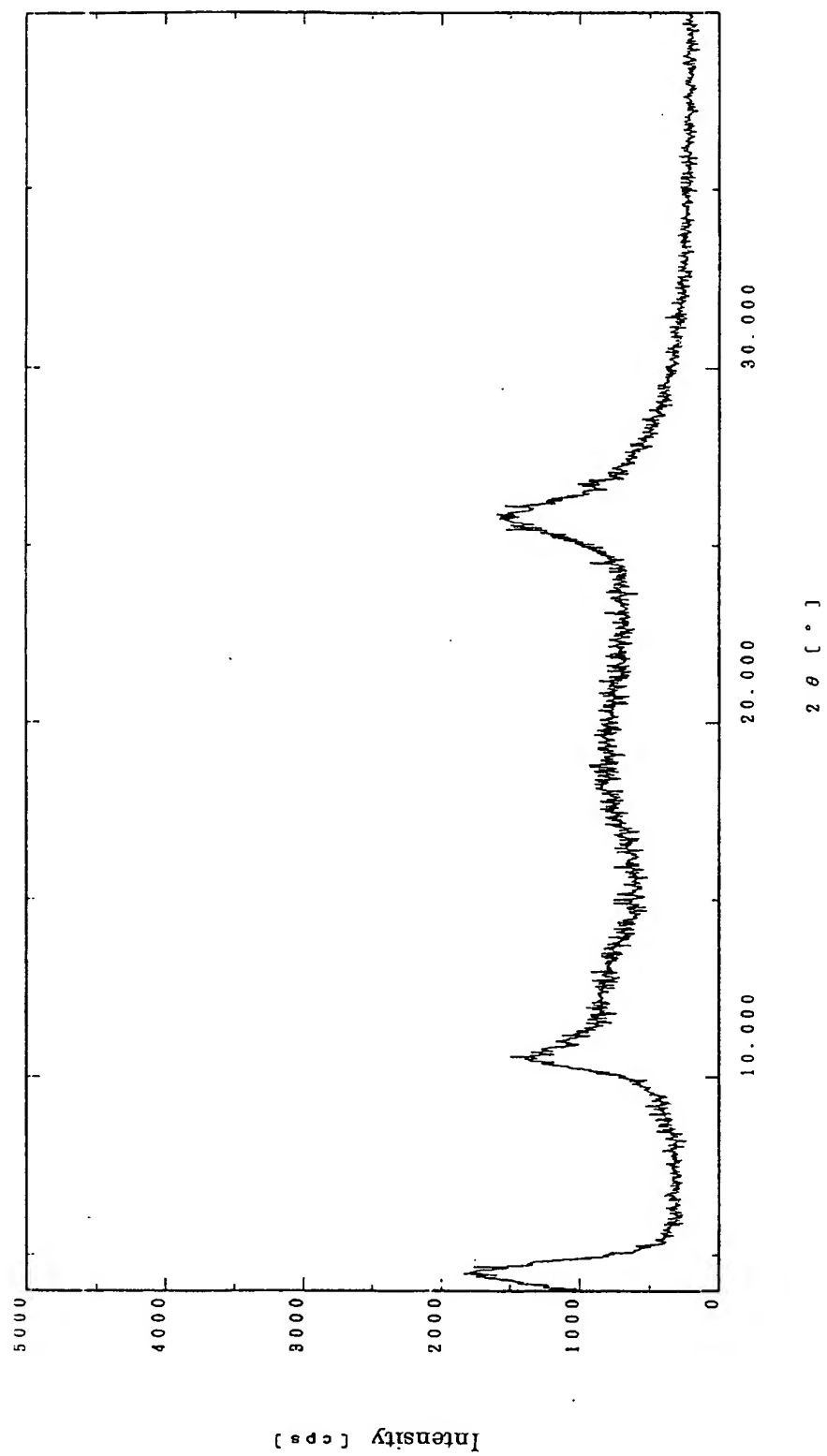




Chart 2

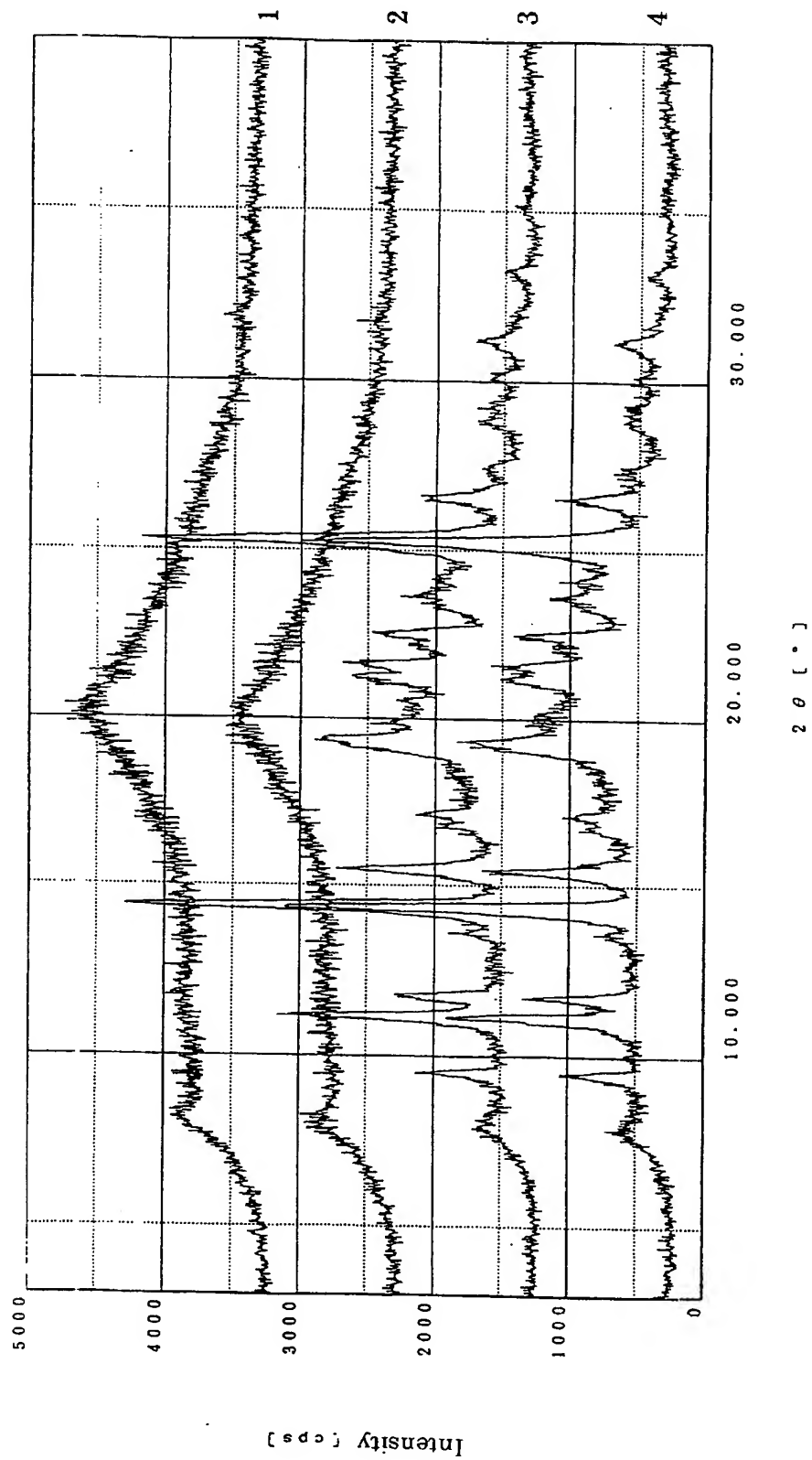


Chart 3

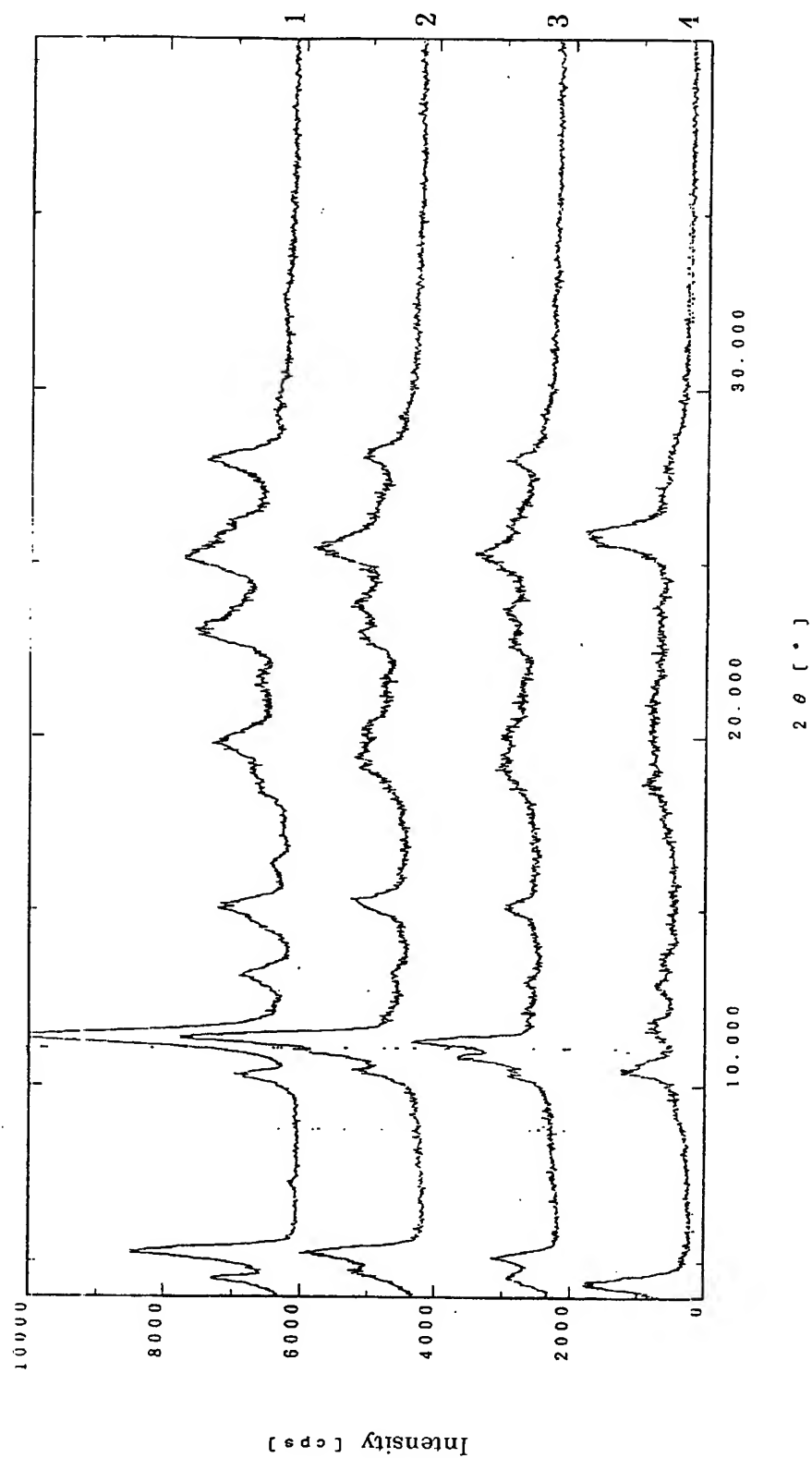




Chart 4

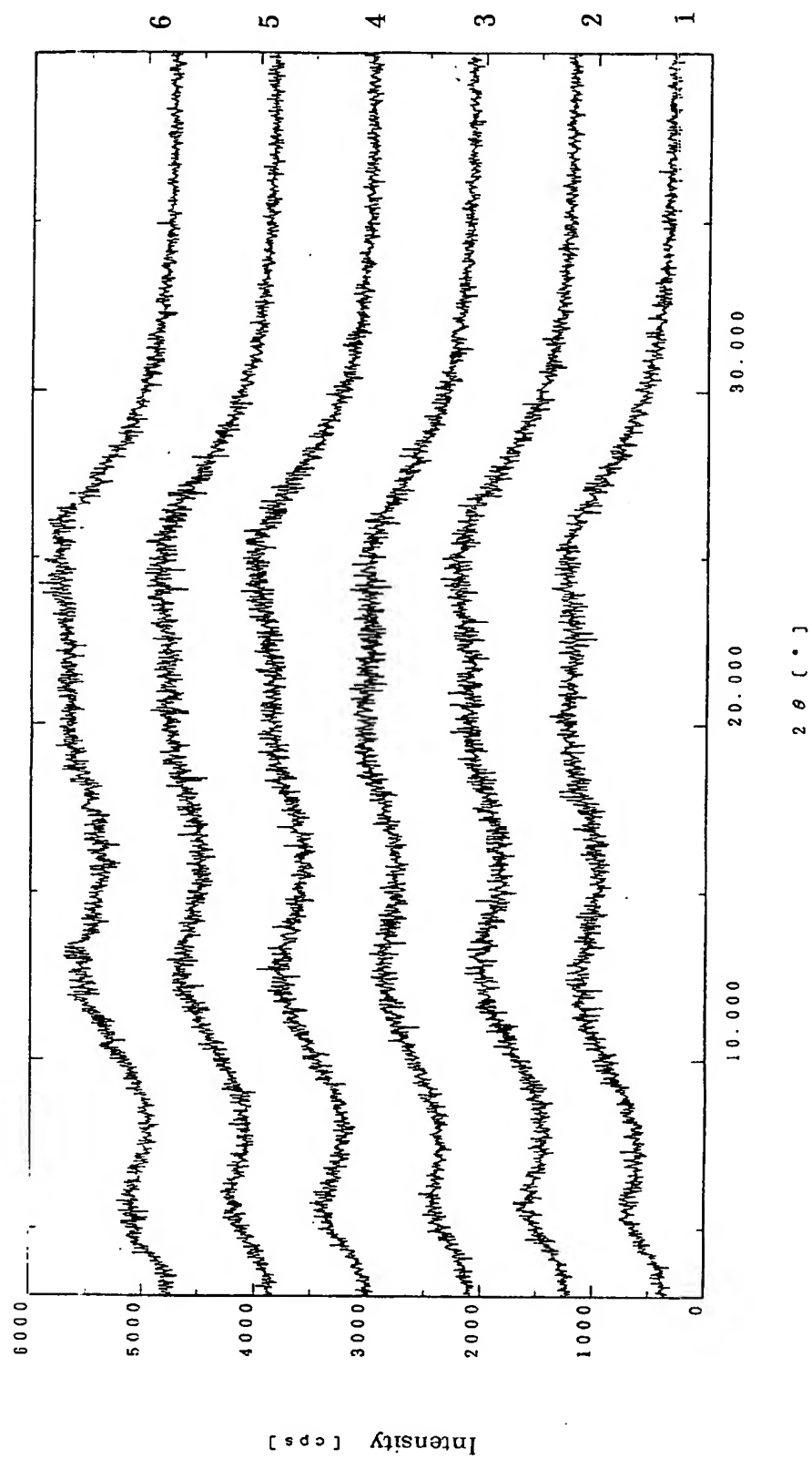


Chart 5

